Award Number: W81XWH-12-2-0137

TITLE: A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD

PRINCIPAL INVESTIGATOR: Steven L. Batki, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA 94121-1545

REPORT DATE:OCTOBER 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2015	Annual	30 Sep 2014 - 29 Sep 2015

4. TITLE AND SUBTITLE

A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-2-0137

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Principal Investigator: Steven L. Batki, MD
Co-investigators: David L. Pennington, Phd; Thomas Neylan, MD; Angela Waldrop, PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

.
Northern California Institute for Research and Education (NCIRE)
San Francisco, CA 94121-1545

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to "self-medicate" or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate's efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI recently completed the first pilot clinical trial of topiramate treatment in veterans with both alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and efficacy in reducing alcohol use. Results also provide support for testing topiramate's potential efficacy in reducing PTSD symptoms.

15. SUBJECT TERMS
Pharmacotherapy, Co-occurring Disorders, PTSD, alcohol dependence, topiramate

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	22	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION:

The overall objective of the project is to improve the care of veterans with alcohol dependence and co-occurring PTSD. The investigators are conducting a controlled clinical trial to test the efficacy of topiramate treatment in reducing alcohol use in patients with PTSD.

Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to "self-medicate" or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate's efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open label trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI recently completed the first pilot clinical trial of topiramate treatment in veterans with both alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and possible efficacy in reducing alcohol use as well as PTSD symptoms.

This project consists of a controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in veterans with these co-occurring disorders. The specific aims are to: 1) definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence; 2) test the efficacy of topiramate to reduce PTSD symptoms; and 3) explore if measures of impulsivity and decision-making predict treatment response and improve with topiramate therapy. To achieve these aims, we are conducting a prospective randomized double-blind controlled parallel-groups clinical trial of topiramate or placebo up to 300 mg per day, combined with weekly alcohol counseling, over a 12-week treatment period with a week 16 follow-up. The study population will consist of 150 male and female veterans between the ages of 18-69 who have concurrent diagnoses of alcohol dependence and PTSD. Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments. The primary treatment outcome will be the percent of days of heavy drinking; the secondary outcome will be PTSD symptom severity. Exploratory measures will include assessments of impulsivity and decision-making.

A.1. PRIMARY AIM: To determine if topiramate treatment reduces alcohol use in veterans with PTSD

1.a. The primary aim is to definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence.

1.b. The primary outcome will be the percent of heavy drinking days over the course of the study as measured by the Timeline Followback.
1.c. The primary hypothesis is that topiramate treatment will be more efficacious than placebo in reducing the proportion of heavy drinking days.

This hypothesis will be tested through a mixed-model statistical analysis of the between-groups differences in the proportion of heavy drinking days over the course of the clinical trial.

A.2. SECONDARY AIMS: To determine if topiramate reduces PTSD symptoms and alcohol use (using other alcohol use measures) in these patients.
The *secondary aims* are*:*
2.1.a To determine whether topiramate will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL); and to determine whether topiramate will be more efficacious than placebo.
2.2.a To determine whether topiramate treatment will be associated with significant reductions in other alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving, and urine Ethyl Glucuronide [EtG]) from baseline to end of treatment; and to determine whether topiramate will be more efficacious than placebo

The *secondary hypotheses* are:
2.1.b Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing TBI treatment as usual --will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL) from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in PCL scores compared to placebo controls.
2.2.b Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing PTSD treatment as usual --will be associated with a significant reduction in scores of other alcohol use measures from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in scores on various alcohol use measures compared to placebo controls.

These hypotheses will be tested:
2.1.c Through a mixed-model statistical analysis of the within-topiramate group and between-groups differences in PCL scores over the course of the clinical trial.
2.2.c Through a mixed-model statistical analysis of the within-topiramate group and between-groups analysis differences in scores on alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving and urine Ethyl Glucuronide [EtG]) over the course of the clinical trial.

A.3. EXPLORATORY AIMS:
The exploratory aims are:
3.1 Measure impulsivity, decision-making, and risk-taking at baseline to assess the relationship between these domains and:
- alcohol use at baseline
- alcohol use over the course of the study

3.2 Assess the relationship between *changes* in alcohol use over the course of the study and *changes* in:

- impulsivity
- risk-taking
- decision-making

3.3 Assess the effects of topiramate versus placebo treatment on:

- impulsivity
- risk-taking
- verbal fluency, verbal memory

The exploratory hypotheses are:
3.1 High impulsivity, high risk-taking, and poor decision-making at baseline will be associated with higher levels of alcohol use at baseline and over the course of the study;
3.2 Reductions in alcohol use will be associated with reductions in impulsivity and risk taking, and improvement in decision-making;
3.3 Topiramate will be associated with greater reductions in impulsivity and risk-taking, but also with greater impairment of verbal fluency and memory than placebo.

These hypotheses will be tested with mixed models similarly to the primary and secondary hypotheses.
3.1 is assessed by the effect of baseline impulsivity and risk-taking (tested separately) on alcohol use over time.
3.2 is tested by estimating subject-specific slopes from random coefficients mixed models predicting changes in alcohol use, impulsivity, and risk-taking, and calculating the Pearson correlation coefficients between slopes of change in alcohol use and changes in impulsivity and risk-taking.
3.3 is tested by the Group by Time interaction term in the mixed models predicting impulsivity, risk-taking, verbal fluency and verbal memory, from treatment group and time, with baseline values as covariates.

BODY:

This study was initiated 29 September 2012. Year 2 of this project covers the time period September 30, 2013 through September 29, 2014. As of September 29, 2014 we have met our overall Year 2 goals in terms of maintaining all regulatory approvals, hiring staff, and setting up the lab. Additionally, we have continued recruiting subjects and administering study intervention since the 2nd quarter of Year 1. Because recruitment was our main focus in Year 2, we developed many novel recruitment strategies that we'll continue to hone and expand upon as we move into Year 3. Two outstanding tasks leftover from Year 1 were completed: we rolled-out the remaining 20 forms in the Access database/interface and employed a 3rd Study Coordinator to bolster recruitment efforts. All tasks for Year 2 were predetermined in the approved Statement of Work; the steps taken to accomplish these tasks are outlined in further detail below.

STATEMENT OF WORK - TIMELINE

TIMELINE AND COST		YR1				YR2				YR3				YR4			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Obtain scientific regulatory approvals (4 months; Mos. 1 to 4)																	
Hire staff, set up lab (4 months; Mos. 1 to 4)																	
Recruit subjects (34 months; Mos. 5 to 38)																	
Conduct 12-week intervention & Wk 16 follow-ups (37 months; Mos. 5 to 41)																	
Collect data on 150 human subjects (37 months; Mos. 5 to 41)																	
Score and analyze data (2 months; Mos. 42 to 43)																	
Write/publish final report (5 months; Mos. 44 to 48)																	
Estimated Budget Year ($K)	Direct	$489,792				$545,546				$576,425				$507,619			
	Indirect	$254,692				$283,684				$299,741				$263,962			

Proposed Timeline
Actual Timeline

Task 1

Test the hypothesis that veterans with alcohol dependence and PTSD assigned to topiramate (TOP) treatment will have fewer heavy alcohol drinking days over the 12 weeks of the treatment trial than subjects receiving placebo (PBO)

Timeline: *Months 1-4:* production and all approvals of human use protocols, hiring staff, start-up/set up lab; *months 5-38:* recruitment of subjects; *months 5-41*: conduct treatment

intervention, follow-ups; *months 5-41*: complete data collection on 150 subjects; *months 42-43*: analyze data; *months 44-48*: final report/manuscripts written and submitted.

TASK 1.a. ***Months 1-4:*** **production and all approvals of human use protocols, hiring staff, start-up/set up lab**

All DOD-funded studies that take place at the San Francisco VA Medical Center are required to receive approval from the local IRB [University of California, San Francisco Committee on Human Research (UCSF CHR)], the VA Clinical Research Workgroup (VA CRW), the Information Security Officer (ISO), the Privacy Officer (PO), the UCSF Clinical and Translational Science Institute (CTSI), the Subcommittee on Research Safety (SRS), and the VA Research and Development Committee (VA R&DC). In addition to gaining approval from the various regulatory bodies, we also applied for a NIH/NIAAA Certificate of Confidentiality (NIH/NIDA CoC), an IND exemption from the Federal Drug Association (FDA) and a Biological Use Authorization (BUA) for Clinical Research from the VA Biosafety Subcommittee as extra protection for our research subjects and study staff. All required approvals were received by 2/26/13 (Month 5).

All regulatory approvals were maintained during Year 2. An informed consent audit from the San Francisco VA Medical Center's Research Compliance Office in March 2014 found our study to be in compliance.

The hiring of lab personnel is complete. As of 10/30/15, we have hired the following essential employees: 1 Lab Manager, 3 Study Coordinators, 1 Research Psychologist, 1 Research Statistician, 1 Research Physician, 1 Research Nurse Practitioner, and 1 Database Developer/Manager. Additional staff that either work at a less percent effort or as volunteers include: 2 Study Physicians, 1 Research Psychologist, 1 Nurse Practitioners, and 1 Data Programmer. We are also supporting a percent effort of our co-investigators. This past year we also brought on a new research volunteer and 6 PhD students/Research Practicum Trainees that have helped with recruitment, pre-screening, brief weekly alcohol counseling, neurocognitive testing, and structured psychological interviews.

The lab set-up is now complete as well. All study staff have been trained on the study protocol and standard operating procedures are in place for clarification and standardization purposes. Both the Access interface/database and the Qualtrics methods of online data collection are complete. All 57 measures and procedures are in active use, and we are now able to monitor drinking and medical data in real time for safety purposes.

TASK 1.b. ***Months 5-38:*** **recruitment of subjects**

Subject recruitment began on 2/27/13 and the first informed consent was signed on 3/20/13. Six hundred and ninety seven potential participants were referred to the study, either by self-referral or by medical/mental health practitioners. All prospective participants were pre-screened for the study; 80 were enrolled (signed informed consent form) and 47 randomly assigned to treatment with topiramate (top) or placebo (PLA). The cohort is mostly male (n=46, 98%) and predominantly Caucasian (n=22, 47%). The planned rate of recruitment was 1 participant per week or 4 participants per month; however, in order to complete recruitment according to schedule, we will need to randomize 9 participants per month over the next 14 months. We are continuously developing new recruitment strategies to meet our enrollment goals.

TASK 1.c. ***Months 5-41*****: conduct treatment intervention, follow-ups**

Inclusion for this study is based on the outcome of a screening phase which includes medical assessment, structured psychological interviews to determine diagnostic eligibility [Structured Clinical Interview for DSM-IV (SCID) and the Clinician Administered PTSD Scale (CAPS)] and additional measures to assess psychiatric severity and medical utilization. Of the 47 participants randomized, 7 (9%) participants dropped out, 8 (17%) participants were withdrawn, and 3 (6%) participants were lost to follow-up. Twenty-five (53%) participants completed the study (as defined by attending the Week 12 visit). Of all participants enrolled, the average number of study visits attended is 9 (81%).

TASK 1.d. ***Months 5-41*****: complete data collection on 150 subjects**

In progress - not complete at this time.

TASK 1.e. ***Months 42-43*****: analyze data**

Not complete at this time.

TASK 1.f. ***Months 44-48*****: final report/manuscripts written and submitted.**

Not complete at this time.

Task 2.

Test the hypothesis that veterans with alcohol dependence and PTSD assigned to topiramate (TOP) treatment will have lower PTSD symptom severity over the 12 weeks of the treatment trial than subjects receiving placebo (PBO)

Timeline**:** ***same as Task 1***

In progress - not complete at this time.

Task 3.

Explore the role of impulsivity and decision-making in the treatment of alcohol dependence and PTSD.

Subtask 3.a. To assess the predictive value of baseline measures of decision-making and impulsivity as related to study retention and alcohol use outcomes.
Subtask 3.b. To test whether reduction in alcohol use is accompanied by reductions in impulsivity/risk-taking and improvement in decision-making in veterans with alcohol dependence and PTSD.
Subtask 3.c. To test whether topiramate is more efficacious than placebo in reducing impulsivity/risk-taking and improving decision-making.

***Design*:** same as Task 1
***Human subjects*:** same as Task 1
Methods: Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments.
Assessments: The exploratory outcomes will be impulsivity/risk-taking as measured by the Balloon Analogue Risk Task (BART) and decision-making as measured by the Delay Discounting Test (DD).

***Outcomes, products and deliverables*:** The *exploratory hypotheses* are:

Subtask 3a: high baseline impulsivity/risk-taking and poor decision-making will be associated with poor retention and worse alcohol use outcome over the course of the trial
Subtask 3b: reductions in alcohol use over the course of the trial will be associated with reduced impulsivity/risk-taking and improved decision-making over the course of the trail
Subtask 3c: topiramate treatment will be more efficacious than placebo in reducing impulsivity and risk-taking and improving decision-making.
These hypothesis will be tested through mixed-model statistical analyses of the between-groups differences in the appropriate measures.

Timeline*:** ***same as Task 1

In progress - not complete at this time.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

None at this time.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; informatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award

PRESENTED ABSTRACTS RELATED TO THIS PROJECT:

Batki, S.L., Meyerhoff, D.J., Spigelman, I., Back, S.E., Pennington, D.L., (Symposium). *Alcohol use disorder and PTSD: From preclinical discoveries to treatment trials*. 38th Annual Research Society on Alcoholism Conference, San Antonio, Texas, 2015.

Pennington, D.L., Meyerhoff, D.J., T. Schmidt, B. Schmeling, B. Lasher, E. Schrodek, S. Yohannes, J. McDonald, E. Herbst, T. Wong, S.L. Batki *Cognitive function in patients with alcohol use disorders with and without PTSD*. 38th Annual Research Society on Alcoholism Conference, San Antonio, Texas, 2015.

B. Schmeling, A. J. Heinz, D. L. Pennington, N. Cohen, B.A. Lasher, E. Schrodek, S. Yohannes, J. McDonald, and S. L. Batki. *An examination of relations between cognitive functioning and alcohol use and craving among veterans with alcohol use disorder and trauma exposure.* 38th Annual Research Society on Alcoholism Conference, San Antonio, Texas, 2015.

E. Schrodek, D. L. Pennington, B. Lasher, E. Herbst, S. Yohannes, J. McDonald, B.L. Schmeling, T. Wong, S.L. Batki. *An evaluation of topiramate treatment: Secondary health outcomes for veterans with alcohol use disorder and comorbid PTSD.* 38th Annual Research Society on Alcoholism Conference, San Antonio, Texas, 2015.

S. Yohannes, D. L. Pennington, B. Lasher, E. Schrodek, J. McDonald, B.L. Schmeling, T. Wong, I. Lee, S.L. Batki. *Pharmacotherapy clinical trial recruitment of veterans with alcohol use disorder and comorbid PTSD/mTBI*. 38th Annual Research Society on Alcoholism Conference, San Antonio, Texas, 2015.

MANUSCRIPTS IN SUBMISSION FOR PEER REVIEW RELATED TO THIS PROJECT:

Heinz, A., Pennington, D.L., Cohen, N., Schmeling. B., Lasher, B., Schrodek, E., Hong, E., Batki, S. Relations between cognitive functioning and alcohol use and craving: An examination among military veterans with alcohol use disorder and trauma exposure. Psychology of Addictive Behaviors.

PRESENTATION AT MOMRP SUSBSTANCE ABUSE IPR IN FT. DETRICK, MD:

Presented overview & progress of study and pilot [W81XWH-05-2-0094] study data.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

There are no conclusions to draw at this time.

REFERENCES: List all references pertinent to the report using a standard journal format (i.e. format used in *Science, Military Medicine*, etc.).

None at this time.

APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, study questionnaires, and surveys, etc.

ALCOHOL USE DISORDER AND PTSD: FROM PRECLINICAL DISCOVERES TO TREATMENT TRIALS -- SYMPOSIUM

Batki, S.L., Meyerhoff, D.J., Spigelman, I., Back, S.E., Pennington, D.L.,

UCSF Department of Psychiatry, Addiction Research Program, San Francisco VA Medical Center, San Francisco, CA 94121; Medical University of South Carolina, Addiction Sciences Division, Charleston, SC 29403 ; UCLA Department of Dentistry, Los Angeles, CA 90095

Chairs/Organizers: Steven L. Batki, M.D. and Dieter J. Meyerhoff, Dr.rer.nat., UCSF

Rationale and Content: Civilian and military personnel with posttraumatic stress disorder (PTSD) frequently suffer from comorbid alcohol use disorders (AUD; Baker et al., 2009). According to the National Comorbidity Survey (Kessler et al., 1996), PTSD was the most frequently occurring anxiety disorder, second only to major depressive disorder, affecting almost 6% of respondents diagnosed with alcohol abuse and almost 8% of alcohol dependent individuals. The survey further shows that the probability of attending a substance abuse treatment program is greater for AUD individuals without comorbid psychiatric disorders than for those with such disorders, including PTSD (Wu et al., 1999). The co-occurrence of AUD and PTSD is associated with poor psychosocial and medical outcomes, high rates of hospitalization, and impaired psychosocial functioning, including relapse to substance use (McCarthy and Petrakis, 2010). Nevertheless, many people with comorbid AUD and PTSD do not receive the specialized treatment that addresses both conditions, partially because the efficacy of treatment options for patients with this dual diagnosis is largely unknown.

AUD has a bidirectional relationship with PTSD. AUD is a known risk factor for the development of PTSD as well as a moderator of PTSD symptom severity. However, AUD is also a potential consequence of PTSD. AUD and PTSD share some common neurobiological mechanisms, e.g. elevations and dysregulation of norepinephrine and glutamate (Strawn & Geracioti, 2008; Norman et al 2011). Alcohol is the most commonly abused substance in patients with PTSD, and for some patients alcohol use may be an attempt to “self-medicate” or cope or to respond to symptoms such as insomnia, anxiety, and hyperarousal (Ouimette et al., 2010; Leeies et al., 2010). A better understanding of the basic pathologic mechanisms in each of these two disorders and of potential specifics of the comorbid condition is required in order to inform the design of more advanced psychotherapies and pharmacotherapies of AUD in co-occurring PTSD. To this end, we have assembled a panel of distinguished speakers who will discuss a wide range of state-of-the-art research from preclinical and neuroimaging applications to psychological and pharmacological therapies in comorbid AUD and PTSD.

Introduction: **Dieter J. Meyerhoff, PhD**, will present the rationale for this symposium, and he will introduce the contributing speakers and the discussant.

Presentation 1: **Symptoms, mechanisms, and alcohol drinking in rodent PTSD models, Igor Spigelman, PhD**
Dr. Spigelman from UCLA will discuss his rat model of stress-enhanced fear learning which mimics several PTSD features, including increased voluntary alcohol intake, and set it in context to other rodent PTSD models.

Presentation 2: **Magnetic Resonance Spectroscopy, Neurocognition, Risk-Taking and Impulsivity in Comorbid AUD and PTSD; David Pennington, PhD**
Dr. Pennington from the San Francisco VA Medical Center will present human data on the relationships between magnetic resonance spectroscopy-derived brain metabolite concentrations, neurocognitive functioning, PTSD symptom severity and alcohol use.

Presentation 3: **Psychological Therapies for Alcohol Use Disorders and PTSD. Sudie E. Back, PhD**
Dr. Back from MUSC will discuss psychological therapies and present data from recent research on combined relapse prevention and exposure-based interventions in the treatment of AUD and PTSD.

Presentation 4: **Pharmacologic Therapies for Alcohol Use Disorder and PTSD, Steven L. Batki, MD**
Dr. Batki from UCSF and the VA Medical Center will review recent research on the pharmacotherapy of co-occurring AUD and PTSD and present findings from a controlled trial of topiramate treatment in comorbid patients. Topiramate has been shown previously to reduce alcohol use in AUD and PTSD symptoms in PTSD patients.

Discussant/Question Moderator: **Dr. Ismene Petrakis** from Yale will serve as Discussant and Moderator of the question period.

COGNITIVE FUNCTION IN PATIENTS WITH ALCOHOL USE DISORDERS WITH AND WITHOUT PTSD

Pennington, D.L., Meyerhoff, D.J., T. Schmidt, B. Schmeling, B. Lasher, E. Schrodek, S. Yohannes, J. McDonald, E. Herbst, T. Wong, S.L. Batki

UCSF Department of Psychiatry, Addiction Research Program, San Francisco VA Medical Center, San Francisco, CA 94121

Purpose: Cognitive dysfunction is commonly observed in both Alcohol Use Disorder (AUD) and Posttraumatic Stress Disorder (PTSD) and is associated with worse treatment outcome. Impairment in impulsivity, risk taking and decision making represent potential targets for AUD treatment intervention. However, there are few studies of cognition in patients with co-occurring AUD and PTSD and there are no studies comparing cognition in patients with both AUD and PTSD to those with AUD alone.

Methods: We assessed 160 patients seeking treatment for AUD; 72 (4 female) with comorbid PTSD and AUD (PAUD), and 88 (12 female) with AUD (ALC) only. Groups were compared on domains of cognition including processing speed, working memory, and auditory-verbal learning and recall and in domains of executive functioning including cognitive flexibility, cognitive inhibition, response inhibition, choice inhibition, risk-taking, and decision making. Groups were also compared on a self-report measure of impulsivity (Barratt Impulsivity Scale). Cognitive domains were correlated with mean standard alcoholic drinks consumed per week in the 90 days prior to assessment.

Results: PAUD and ALC were similar in education, age, smoking frequency, and mean standard alcoholic drinks consumed per week in the 90 days prior to assessment (61±43 vs. 59±42, respectively). However, at time of testing, PAUD had fewer days abstinent compared to ALC (6±9 vs. 28±10, respectively). PAUD performed significantly worse than ALC on tasks measuring cognitive inhibition, risk-taking, working memory, auditory-verbal learning and recall with moderate to large effect sizes (all $p<0.02$; Cohen's $d=0.45$-1.48). Surprisingly, PAUD performed significantly better in cognitive flexibility ($p=0.005$). Controlling for days abstinent did not significantly alter the results. PAUD also reported worse attentional, motor and non-planning impulsivity than ALC ($p<0.001$). Among PAUD, more alcohol consumption was correlated with worse auditory-verbal learning and more risk taking. Alcohol consumption did not correlate with cognition in the ALC group.

Conclusions: Findings suggest that patients presenting to treatment with comorbid PTSD and AUD have worse cognitive functioning than patients with AUD alone, particularly in domains necessary to cease substance use such as cognitive inhibition and risk-taking. Interventions which target these cognitive domains may be particularly beneficial to patients with co-occurring AUD and PTSD.

Acknowledgment: Department of Defense (DOD) # W81XWH-12-2-0137, CDMRP PH TBI; DOD # W81XWH-05-2-0094; DOD # W81XWH-11-2-0245.

AN EXAMINATION OF RELATIONS BETWEEN COGNITIVE FUNCTIONING AND ALOCHOL USE AND CRAVING AMONG VETERANS WITH ALCOHOL USE DISORDER AND TRAUMA EXPOSURE

B. Schmeling, A. J. Heinz, D. L. Pennington, N. Cohen, B.A. Lasher, E. Schrodek, S. Yohannes, J. McDonald, and S. L. Batki.

UCSF Department of Psychiatry, Addiction Research Program, San Francisco VA Medical Center, San Francisco, CA 94121

Purpose: Cognitive dysfunction is commonly observed among individuals with Alcohol Use Disorder (AUD) and Posttraumatic Stress Disorder (PTSD) and is, in turn, associated with worse treatment outcomes. Accordingly, disruptions in cognitive functioning may be conceptualized as a trans-disease phenomenon representing a potential high-yield target for intervention. The purpose of this study was to examine relations between different cognitive functions and alcohol use and craving among U.S. military Veterans with AUD and trauma exposure.

Methods: Participants were 68 male and female Veterans with AUD (SCID DSM-IV) and trauma exposure (Life Events Checklist) entering treatment to reduce alcohol use. Participants completed measures assessing alcohol use (Timeline Follow Back) and craving (Obsessive Compulsive Drinking Scale), PTSD symptom severity (PCL), and cognitive functioning (executive functioning [Trail Making Test B], risk-taking/impulsivity [Balloon Analogue Risk Task], and verbal learning and memory [Hopkins Verbal Learning Test-Revised]). Three step-wise regressions were performed to assess variance explained by PTSD symptoms and cognitive functions in quantity and frequency of alcohol use and alcohol craving.

Results: Alcohol craving and quantity of alcohol consumption, but not frequency, were positively correlated with PTSD symptom severity and symptom clusters. In addition, higher risk-taking/impulsivity was associated with greater PTSD symptom severity and cluster C symptoms (avoidance and numbing). After controlling for PTSD symptom severity, poorer learning and memory was associated with higher quantity and frequency alcohol consumption in the 90 days prior to treatment and risk-taking/impulsivity was positively associated with alcohol craving.

Conclusions: Findings suggest that interventions to strengthen cognitive functioning might be used as a preparatory step to augment empirically supported treatments for AUD. Clinicians are also encouraged to consider a standard assessment of cognitive functioning, in addition to PTSD severity, in treatment planning and delivery for this vulnerable and high-risk population.

Acknowledgments: This project was supported by Department of Defense W81XWH-05-2-0094, W81XWH-12-2-0137, and W81XWH-11-2-0245 (SLB), administered by the Northern California Institute for Research and Education. Support was also provided by a VA Rehabilitation Research and Development (RR&D) Career Development Award – 2 (1IK2RX001492-01A1) granted to Dr. Heinz.

AN EVALUATION OF TOPIRAMATE TREATMENT: SECONDARY HEALTH OUTCOMES FOR VETERANS WITH ALCOHOL USE DISORDER AND COMORBID PTSD

E. Schrodek, D. L. Pennington, B. Lasher, E. Herbst, S. Yohannes, J. McDonald, B.L. Schmeling, T. Wong, S.L. Batki

San Francisco Veteran Administration Medical Center and Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

Purpose: Recent evidence shows that topiramate treatment may be effective in reducing alcohol consumption and PTSD symptoms in veterans with co-occuring alcohol use disorder (AUD) and PTSD (Batki, 2014). There is also evidence that topiramate has positive secondary health outcomes in reducing hypertension and body mass index (BMI) in those with AUD only (Johnson, 2008). We sought to determine whether topiramate could reduce blood pressure, weight and BMI in a veteran population with comorbid AUD and PTSD.

Methods: This was a secondary analysis of a prospective 12-week, randomized, double-blind, placebo-controlled pilot trial of flexible-dose topiramate up to 300 mg/day in 30 veterans with PTSD and AUD. We tested the efficacy of topiramate vs. placebo in the reduction of secondary outcomes including systolic and diastolic blood pressure, weight, and BMI. Outcome measures were correlated with alcohol consumption and PTSD symptom severity measures (PCL-Checklist) at baseline and week 12.

Results: Topiramate was more efficacious than placebo in reducing systolic (mean difference, 11.09 mm Hg; 95% CI, 3.64-18.54; p=.005) and diastolic (mean difference, 6.32 mm Hg; 95% CI, 0.34-12.29; p=.039) blood pressure from pre-hypertensive to normal levels in patients with comorbid AUD and PTSD. There was also a trend for a treatment-by-week interaction for weight (F(1,28= 1.82, p=.079). Topiramate participants significantly lost weight between baseline and week 6 (average weight loss, 1.8 kg/4.0 lbs; p=.009), and then gained weight between week 6 and 12 (average weight gain, 2.2 kg/4.9 lbs; p=.009), whereas the placebo group did not show any significant change during these time intervals. BMI results were similar to weight. At baseline, higher re-experiencing and total PTSD symptom severity were associated with heavier weight. At week 12, greater alcohol consumption and heavy drinking frequency was associated with higher blood pressure.

Conclusions: Topiramate appears to be efficacious in reducing blood pressure from pre-hypertensive to normal levels, but not in producing lasting weight loss in veterans with AUD and PTSD. Results require replication in a larger study.

Acknowledgment: Department of Defense (DOD) # W81XWH-12-2-0137, CDMRP PH TBI; DOD # W81XWH-05-2-0094; DOD # W81XWH-11-2-0245.

PHARMACOTHERAPY CLINICAL TRIAL RECRUITMENT OF VETERANS WITH ALCOHOL USE DISORDER AND COMORBID PTSD/mTBI

S. Yohannes, D. L. Pennington, B. Lasher, E. Schrodek, J. McDonald, B.L. Schmeling, T. Wong, I. Lee, S.L. Batki

San Francisco Veteran Administration Medical Center and Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

Purpose: Veterans with alcohol use disorder (AUD), comorbid PTSD and mild traumatic brain injury (mTBI) have been dramatically underrepresented in psychopharmacology clinical trial treatment research. One contributing factor is the difficulty faced in recruiting these complex patients. To identify effective recruitment strategies, we examined the yield of various sources of participants in two randomized controlled trials of topiramate treatment in veterans with AUD and PTSD/ mTBI.

Methods: We assessed the yield of different strategies for recruitment of veterans with AUD/PTSD/mTBI. Sources of potential participants included primary care and mental health clinicians, direct mailings to veterans identified with AUD/PTSD/mTBI per medical record searches, fliers, clinical research database searches, direct referrals from other studies, and intake screening forms distributed in primary care, substance use, and mental health clinics at the San Francisco Veteran Administration Medical Center.

Results: 801 potential participants were identified through a variety of means over 21 months. 161 (20% of total) qualified for prescreening, which yielded 77 (9% of total) who were consented for in-depth screening procedures. In total, 49 (6% of total) passed screening and were enrolled. The highest yield referral sources were clinician referrals (37%), fliers (27%), and mailings (16%). Of the 49 (1 female) enrolled, mean age was 50.7±12.4 with 13.3±1.6 years of education. Of those consented, the most frequent reasons for screening out were failure to meet full eligibility criteria, psychiatric instability, and being lost to follow-up. Enrolled veterans were primarily from Vietnam (32.7%) and Iraq/Afghanistan (30.6%) conflicts, 44.9% combat exposed. Participants consumed 64.7±48.4 standard alcoholic drinks per week in the 90 days prior to screening. Baseline PTSD severity was 71.9±22.5 (Clinician Administered PTSD Scale) and depression severity was 24.5±11.1 (Beck Depression Inventory).

Conclusion: Recruitment of veterans with AUD and comorbid PTSD or mTBI is challenging and requires a large expenditure of resources. Only 49/801 (6%) potential participants progressed to enrollment. Fliers were a minimal effort and high yield referral source. Primary care and mental health clinicians were the most successful sources of potential participants, suggesting that close relationships with these clinics is essential to recruitment.

Acknowledgment: Department of Defense (DOD) # W81XWH-12-2-0137, CDMRP PH TBI; DOD # W81XWH-05-2-0094; DOD # W81XWH-11-2-0245.

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

Data analyzed for DSMB Meeting (8/31/15)

Demographics of Randomized Participants, as of 8/31/15

Mean Age, years	54.8

Gender	N (percent)
Male	45 (98%)
Female	1 (2%)

Ethnicity	N (percent)
Latino/Hispanic	13 (28%)
Non-Latino	33 (72%)

Race	N (percent)
Asian and Pacific Islander	1 (2%)
Black/African American	12 (26%)
Mixed	10 (22%)
Native American	1 (2%)
White	21 (46%)
Unknown/Not reported	1 (2%)

TIME LINE FOLLOW BACK: BASELINE DRINKING (PAST 90 DAYS), AS OF 8/31/2015

Drinking Aggregate	Mean ± Standard Deviation
Average Drinking Days per Week	5.3 ± 1.8
Average Heavy Drinking Days per	4.5 ± 2.3
Average Drinks$ per Drinking Day	12.7 ± 8.7
Average Drinks$ per Week	64.9 ± 50.8

-Data has not finished quality check
-Heavy Drinking Day (>4 standard alcoholic drinks for men, >3 alcoholic drinks for women)
$ standard alcoholic drink defined as containing 13.6 g of pure alcohol

TOTAL ADVERSE EVENTS (PERCENT), AS OF 8/31/2015* (n=46)**

Adverse Event Organ System and Dictionary Term (MedDRA)	Baseline Adverse Events n (%)	Treatment Emergent Adverse Events n (%)
Neurologic		
Numbness/Tingling	29 (63)	8 (17)
Taste	5 (11)	16 (35)
Difficulty with Concentration/Attn	38 (83)	3 (7)
Difficulty with Memory	37 (80)	4 (9)
Slow Thinking	30 (65)	8 (17)
Confusion	17 (37)	9 (20)
Language Problems	24 (52)	4 (9)
Systemic		
Fatigue	32 (70)	8 (17)
Loss of Appetite	11 (24)	16 (35)
Dizziness	18 (39)	10 (22)
Itching	21 (46)	8 (17)
Sleepiness	30 (65)	11 (24)
Psychiatric		
Nervousness	40 (87)	3 (7)
Depression	39 (85)	3 (7)
Suicidal Thoughts	7 (15)	1 (2)
Gastrointestinal		
Diarrhea	13 (28)	21 (46)
Ophthalmologic		
Abnormal Vision	14 (30)	11 (24)
Eye Pain	6 (13)	6 (13)

NOTE: Not all participants completed 12 weeks of study at time of analysis.
***Data has been entered but not cleaned

*****Data has been entered but not cleaned**